



CORRELATION OF CELLULAR AND MOLECULAR CHANGES IN SPUTUM OF PATIENTS SUSPECTED OF PULMONARY TUBERCULOSIS WITH DIABETES AND NON-DIABETES

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ABSTRACT

Objective: Pulmonary tuberculosis (TB) remains a main global health concern, cellular and molecular changes in sputum, containing neutrophil and lymphocyte proportions, total leukocyte count, ESR, and glycemic status, provide insights into disease activity. Therefore, the present study evaluated the correlation of these cellular and molecular parameters in suspected pulmonary TB patients and to compare patterns between diabetic and non-diabetic individuals.

Methodology: This cross-sectional experimental study was performed in institute of Basic Medical Sciences (IBMS), Khyber Medical University. A total of 110 patients aged ≥ 18 years suspected with pulmonary tuberculosis, divided into two groups on the basis of their diabetic status: with Diabetes ($n = 55$) and without Diabetes ($n = 55$), were included in the study. A chi-square test was used to determine the association of cellular and molecular findings between both groups. In addition, the correlation between the mean of the demographic variables in groups was determined using a Mann Whitney test. Pearson and Spearman correlation and rank correlation were determined to find out the correlations among cellular and molecular parameters.

Results: The results indicated that strong relationships were observed between neutrophils and lymphocytes with diabetic ($r = -0.999$, $p < 0.001$) and non-diabetic patients ($r = -0.995$, $p < 0.001$), and they appear to be inverse in nature. The TLC was found to be positively correlated with the ESR among non-diabetic patients (0.464 , $p < 0.001$). There was a positive correlation between fasting blood sugar (FBS) and ESR, but statistically significant (0.434 , $p < 0.001$). **Conclusion:** This research found that there was a significant negative linearity between neutrophils and lymphocytes in suspected tuberculosis patients of pulmonary complications whether or not patients were diabetic. In diabetic patients, a positive association was found between ESR and fasting blood sugar, demonstrating that high levels of glycemic control and increased inflammatory response are related.

Keywords: Pulmonary Tuberculosis, cellular and molecular changes, neutrophils, lymphocytes.

INTRODUCTION

Tuberculosis (TB) is one of the significant world issues of public health despite the constant measures of its control. The most recent World Health Organization (WHO) Global Tuberculosis Report

estimated that TB developed in 10.8 million people and about 1.23 million deaths were reported due to the disease in 2023; TB is still considered one of the most frequent causes of infectious disease-related deaths in the world ⁽¹⁾. *Mycobacterium tuberculosis* is the cause of the disease; it is a bacterium, which is transmitted as aerosolized droplet during sneezing and cough of people with active pulmonary TB. It is estimated that a quarter of the entire world population carries the latent TB infection, and a percentage of the population develops the active disease, pulmonary being the most common and infectious ⁽²⁾.

TB has a significant geographic heterogeneity in its prevalence in the world. South-East Asia, Africa and Western Pacific are high-burden regions and the countries' South-Eastern Asia like India, Indonesia, China, Philippines and Pakistan have a considerable share in the incident cases ⁽³⁾. In Pakistan, the private sector (providing 84 percent of all healthcare) has only been able to diagnose and treat 55 percent of the estimated TB burden and only 18 percent of drug-resistant cases in 2021. Despite an increase in involvement of the private sector in case detection to 40% and over-90 percent success of treatment of drug-susceptible TB, significant gaps such as low bacteriological confirmation, incomplete drug-resistance testing, funding inadequacies, lack of effective data systems, and weak inter-provincial coordination still prevail and thus continue to hinder effective control of TB ⁽⁴⁾.

Diabetes mellitus (DM) is one of the comorbidities that have become critical and affecting the epidemiology of TB. The prevalence of diabetes has been on the rise in the world over the past decades and especially in low and middle income nations where the TB prevalence is still high. Diabetes changes the host immunity, becoming more susceptible to *M. tuberculosis* and active disease development. Research indicates that diabetes may increase the likelihood of having active TB by three times and is a risk factor that leads to more severe clinical manifestations, delayed bacteriological conversion of sputum, impaired treatment and high relapse rates ⁽⁵⁾. One systematic review has provided the level of TB-DM comorbidity burden: it was estimated that about 13.7% of patients with pulmonary TB also have diabetes mellitus ⁽⁶⁾.

Diabetes disease is one of the highest in the world, and tens of millions of adult people are affected in Pakistan. This margin of disease control is an uphill task to TB and diabetes epidemics. The recent epidemiological studies identify positive variability in the prevalence of diabetes in TB patients and is a reflection of the discrepancy in study groups and methods of diagnosis, and consistently reflects a greater burden of DM in pulmonary TB cohorts relative to non-TB cohorts ⁽⁷⁾. The dual epidemic is especially problematic as hyperglycemia and immune dysregulation in diabetes undermine host defense systems, which are needed to contain *M. tuberculosis*, including macrophage phagocytosis and cytokine signaling ⁽⁸⁾.

Better insights of cell and molecular modifications in the sputum of individuals having suspect pulmonary TB is essential in enhancing diagnostic and prognostic interventions. The main excretion of pulmonary TB, sputum, contains bacilli, but also macrophages and cellular evidence as well as evidence as molecular products, which represent the current host-pathogen interaction. The presence of quantitative and qualitative modifications in inflammatory mediators, immune cells profile, and bacteria loads in sputum may demonstrate information about the severity and the evolution of the disease. These cellular and molecular signatures might not be identical in diabetic tuberculosis patients because of poor immunity, dysregulated cytokines, and alteration in metabolic pathways that can affect diagnosis accuracy and monitoring of treatments ⁽⁹⁾.

Pulmonary TB is normally diagnosed using standard methods such as sputum smear microscopy, acid-fast bacilli, nucleic acid amplification techniques, such as GeneXpert MTB/RIF, culturing, and chest radiography. The sensitivity and specificity of such tools differ, and their functionality may be influenced by comorbid entities (including diabetes that alters bacterial load and host reactions in sputum) ⁽¹⁰⁾. The multi-drug antituberculosis therapy used in treating pulmonary TB extends not less than 6 months, i.e. using isoniazid, rifampicin, pyrazinamide and ethambutol, treatment response is pegged on adherence and good immune response. Diabetes also complicates the management because

it puts at risk with adverse outcomes and demands combined interventions that deal with glycemic control and TB treatment (5).

The importance of studying changes in cells and molecules in sputum, especially in subgroups involved and without diabetes, is to enhance the accuracy of the diagnosis, pathophysiology disparities, and biomarkers that predict their response to the treatment. Improved sputum parameter characterization might be used to detect patients earlier, stratify by risk, and manage better populations with a high prevalence of TB and diabetes.

This study therefore aims to correlate cellular (e.g., immune cell differentials and bacillary load) and molecular (e.g., cytokines, host-response biomarkers) changes in sputum of patients suspected of pulmonary TB, comparing those with and without diabetes, to elucidate differences that could inform clinical practice and public health interventions in high-burden settings.

METHODOLOGY

This cross-sectional experimental study was performed in institute of Basic Medical Sciences (IBMS), Khyber Medical University, and samples were gathered from Khyber Teaching Hospital, Lady Reading Hospital Peshawar and Rehman Medical Complex, Peshawar. The duration of study was from May 2025 to July 2025. The Ethical approval was obtained from the Ethical Review Committee. A total of 110 patients aged ≥ 18 years with suspected pulmonary tuberculosis based on cellular and molecular findings; and willingness to participate in the study were included. Patients were divided into two groups on the basis of diabetic status: with Diabetes ($n = 55$) and without Diabetes ($n = 55$). While, patients with extrapulmonary TB only, inadequate medical records, previous anti-TB treatment within the last six months, concomitant immunocompromised disease excluding diabetes (e.g., HIV), and those with severe systemic diseases were excluded from the study.

Demographic details, clinical symptoms, and related medical history were collected using a structured proforma. Demographic variables included age groups, gender, weight, and height. Clinical variables included a history of tuberculosis, presence of a chronic condition, status of the BCG scar, and current medication use along with present clinical symptoms such as cough, fever, weight loss, and lack of appetite. Bio-markers included the measurement of cellular parameters with the help of bronchoalveolar lavage (BAL) where the percentages of neutrophils and lymphocytes were observed. Hematological and molecular variables include total leukocyte count (not in the norm, mildly, moderately, or severely high), erythrocyte sedimentation rate (not in the norm, mild, moderate and high), fasting blood sugar level (not in the norm, diabetic range, and untreated).

The SPSS version 23.0 was used to analyze the data. The frequencies and percentages (demographic details and signs and symptoms) were used to indicate the numbers. The records of quantitative variables were in the form of means with standard deviations. The relationship between cellular and molecular variables between the two groups was investigated using a chi-square test. Also, a Mann Whitney test was used to determine the analysis of the relationship between the means of demographic variables among groups. The cellular and molecular parameters correlations were evaluated on Pearson correlation between normally distributed data and Spearman rank relationship between non-normally distributed data. The p-value of less than 0.05 was deemed as statistically significant.

RESULTS

A total of 110 patients with suspected pulmonary tuberculosis were included, equally divided into diabetic ($n = 55$) and non-diabetic ($n = 55$) groups. The age distribution showed, with most patients being older than 51 years 28(50.9%) in diabetics and 33(60.0%) in non-diabetics, and an insignificant difference was observed across age groups ($p = 0.354$). Gender distribution was also similar, with males comprising 29(52.7%) of the diabetic group and 30(54.5%) of the non-diabetic group ($p = 0.848$). The mean age, weight, and height did not differ significantly between diabetics and non-diabetics (49.10 ± 11.8 vs. 50.67 ± 13.8 years, $p = 0.240$; 60.98 ± 13.1 vs. 58.05 ± 11.4 kg, $p = 0.693$; 5.45 ± 0.26 vs. 5.42 ± 0.26 feet, $p = 0.696$, respectively). A significantly higher proportion of diabetic patients 10(18.2%) reported taking medications compared to non-diabetics 1(1.8%), ($p = 0.004$).

Similarly, the presence of chronic illness was significantly more common among diabetics 14(25.5%) than non-diabetics 3(5.5%), ($p = 0.004$). However, a history of tuberculosis and the presence of a BCG scar were insignificantly associated between the two groups ($p = 0.495$ and $p = 0.432$, respectively). Regarding clinical symptoms, cough was reported by all patients in both groups 55(100%). Fever was significantly more frequent in diabetic patients 55(100.0%) than non-diabetics 50(90.9%), ($p = 0.022$). Diabetic patients 51(92.7%) also had a significantly higher prevalence of weight loss ($p = 0.003$) and reduced appetite 50(90.9%), ($p < 0.001$) compared to non-diabetic patients 33(60.0%), as depicted in Table I.

The association of cellular and molecular changes among suspected tuberculosis patients stratified by diabetic status revealed that the mean neutrophil percentage was slightly lower in diabetics compared to non-diabetics (52.84 ± 22.5 vs. 56.20 ± 18.1), while lymphocyte percentages were marginally higher in diabetics (47.14 ± 22.6 vs. 44.20 ± 18.36); however, these differences were insignificant ($p = 0.462$ and $p = 0.582$, respectively). Regarding total leukocyte count (TLC), the majority of patients in both diabetics 42(76.4%) and non-diabetics 45(81.8%) having normal TLC values. Mildly and moderately elevated TLC levels were detected in small proportions of both groups, and severe elevation was rare, with insignificant association between TLC categories and diabetic status ($p = 0.605$). In contrast, ESR showed a significant association with diabetes ($p = 0.024$). Normal ESR values were more frequent among non-diabetic patients 39(70.9%) compared to diabetics 24(43.6%). Conversely, moderate to high ESR elevations were more commonly observed in diabetic patients, with 11(20.0%) showing moderate and 13(23.6%) showing high ESR levels, as compared to 5(9.1%) each in the non-diabetic group. Fasting blood sugar levels demonstrated a highly significant difference between the groups ($p < 0.001$). All non-diabetic patients had normal FBS levels (<126 mg/dL). Among diabetic patients, only 12(21.8%) had normal values, while 13(23.6%) were in the diabetic range (126–200 mg/dL) and more than half 30(54.5%) had markedly uncontrolled fasting blood sugar levels (>200 mg/dL), as depicted in table II.

The correlation between cellular and molecular parameters among suspected tuberculosis patients stratified by diabetic status showed that a very strong and statistically significant negative correlation was observed between neutrophils and lymphocytes in both diabetic and non-diabetic patients ($r = -0.999$ and $r = -0.995$, respectively; $p < 0.001$ for both), indicating an inverse relationship between these two BAL cellular components irrespective of diabetic status. Among diabetic patients, TLC showed a weak positive correlation with FBS; however, this association was statistically insignificant ($\rho = 0.070$, $p = 0.612$). In contrast, TLC demonstrated a weak positive but non-significant correlation with ESR in diabetics ($\rho = 0.192$, $p = 0.160$), whereas a moderate and statistically significant positive correlation was observed in non-diabetic patients ($\rho = 0.464$, $p < 0.001$). In addition, FBS showed moderate positive relationship with ESR in diabetic individuals that was statistically significant ($\rho = 0.434$, $p = 0.001$) indicating that high inflammatory activity was related to poorer glycemic control as it is presented in Table III.

Table I: The Demographic Information of Patients Suspected of Pulmonary Tuberculosis (n=110).

Variables		Diabetes Yes (n=55) Mean $\pm$ SD n(%)	Diabetes No (n=55) Mean $\pm$ SD n(%)	p-value
Age group (Years)	15-30	5(9.1%)	7(12.7%)	0.354
	31-50	22(40.0%)	15(27.3%)	
	>51	28(50.9%)	33(60.0%)	
Gender	Male	29(52.7%)	30(54.5%)	0.848
	Female	26(47.3%)	25(45.5%)	
Age (Years)		49.10 $\pm$ 11.8	50.67 $\pm$ 13.8	0.240*
Weight (kg)		60.98 $\pm$ 13.1	58.05 $\pm$ 11.4	0.693*

Height (feet)			5.45 ± 0.26	5.42 ± 0.26	0.696*
Taking any medicine	Yes		10(18.2%)	1(1.8%)	0.004
	No		45(81.8%)	54(98.2%)	
History of TB	Yes		14(25.5%)	11(20.0%)	0.495
	No		41(74.5%)	44(80.0%)	
Chronic illness	Yes		14(25.5%)	3(5.5%)	0.004
	No		41(74.5%)	52(94.5%)	
BCG Scar	Yes		32(58.2%)	36(65.5%)	0.432
	No		23(41.8%)	19(34.5%)	
Clinical symptoms and signs	Cough	Yes	55(100.0%)	55(100.0%)	_____
		No	0(0.0%)	0(0.0%)	
	Fever	Yes	55(100.0%)	50(90.9%)	0.022
		No	0(0.0%)	5(9.1%)	
	Weight loss	Yes	51(92.7%)	39(70.9%)	0.003
		No	4(7.3%)	16(29.1%)	
	Reduced apatite	Yes	50(90.9%)	33(60.0%)	<0.001
		No	5(9.1%)	22(40.0%)	

Mann Whitney test*

Chi square test

Table II: Relationship of cellular and molecular alterations in suspected TB patients (n=110).

Variables		Diabetes Yes (n=55)	Diabetes No (n=55)	p-value
Bronchoalveolar lavage (BAL)	Neutrophils (%)	52.84±22.5	56.20±18.1	0.462*
	Lymphocytes (%)	47.14±22.6	44.20±18.36	0.582*
TLC (Total Leukocyte Count)	Mildly elevated TLC (11000–15000)	9(16.4%)	6(10.9%)	0.605
	Moderately elevated TLC (15001–17000)	4(7.3%)	3(5.5%)	
	Severely elevated TLC (>17000)	0(0.0%)	1(1.8%)	
	Normal (4,000 – 11,000 cells/μL)	42(76.4%)	45(81.8%)	
ESR	Normal (<20 mm/hr)	24(43.6%)	39(70.9%)	0.024
	Mild elevation (20–40)	7(12.7%)	6(10.9%)	
	Moderate elevation (41–60)	11(20.0%)	5(9.1%)	
	High elevation (>60)	13(23.6%)	5(9.1%)	
Fasting blood sugar	Normal (<126 mg/dL)	12(21.8%)	55(100.0%)	<0.001
	Diabetic Range (126–200 mg/dL)	13(23.6%)	0(0.0%)	
	High Uncontrolled (>200 mg/dL)	30(54.5%)	0(0.0%)	

Mann Whitney test*

Chi square test

Table III: Diabetes vs Non-Diabetes Correlation of Cellular and Molecular Changes in Suspected TB Patients

Cellular and molecular findings	Diabetes Yes		Diabetes No	
	Correlation Coefficient (r / ρ)	p-value	Correlation Coefficient (r / ρ)	p-value
Neutrophils vs Lymphocytes	-0.999	<0.001	-0.995	<0.001
TLC vs FBS	0.070*	0.612	-	-
TLC vs ESR	0.192*	0.160	0.464*	<0.001
FBS vs ESR	0.434*	0.001	-	-

Spearman's rank correlation *

Pearson's Correlation

DISCUSSION

This article analyzed cellular and molecular variations in sputum of patients with suspected pulmonary tuberculosis comparing those with and without type 2 diabetes. The patients with diabetes were found to have much higher inflammatory activity in terms of increased ESR and more pronounced clinical symptoms such as fever, loss of weight and loss of appetite. Although the percentages of the neutrophil and lymphocytes did not significantly differ, fasting blood sugar was positively correlated with ESR, and it is possible that inadequate glycemic control contributes to the intensification of inflammatory reactions in TB. These results point to the effects of diabetes on host immune phenotype and clinical manifestation in pulmonary tuberculosis.

The meta-analysis of 24 studies (2,569,451 patients with T2DM) had an incidence of PTB of 129.9 per 100,000 people and prevalence of 511.2 per 100,000 people with the highest incidence and prevalence rates in Asia and other high TB-endemic areas ⁽¹¹⁾. Fifty percent of the suspected PTB patients in our case population of 110 patients were diabetic, which is far exceeded by the global estimate and could probably be a reflection of the high-risk regional population and hospital-acquired environment, demonstrating the need to screen the TB patients regarding diabetes in Pakistan.

Recent analyses among 1,106 pulmonary tuberculosis patients reported that those with diabetes had higher ESR (45.5) and lower PLR and MLR; ESR, MLR, and PLR were independent risk factors, and their combined assessment improved diagnostic accuracy (AUC 0.712), supporting their use in identifying diabetes in PTB patients ⁽¹²⁾. In our study, ESR was elevated in 43.6% of diabetic patients and particularly high (>60 mm/hr.) in 23.6%, compared to 29.1% elevated ESR in non-diabetics, confirming that systemic inflammation is amplified in PTB patients with diabetes.

In a study of 552 patients from Kunming, China, triglycerides, PNR, PMR, MHR, and MLR were significant risk factors for pulmonary TB in diabetics, with a combined model achieving 75.0% sensitivity and 81.9% specificity ⁽¹³⁾. In our cohort, diabetic patients with suspected TB showed elevated ESR (mean 45.5 mm/hr.) and mild-to-moderate leukocytosis (mean total leukocyte count $10.8 \times 10^9/L$), reflecting comparable immune activation patterns.

A study of 200 tuberculosis patients reported a diabetes prevalence of 21.4%, which was higher in females and patients over 50 years of age. Alterations in the inflammatory parameters were also identified in the study and ESR decreased after four months, and RBS and CRP only changed slightly especially among the patients with comorbidities ⁽¹⁴⁾. On the same note our study results indicated a significant ESR difference between diabetic and non-diabetics and also a moderate positive relationship between fasting blood sugar and ESR which indicates increased rates of inflammatory activity in diabetic TB.

Diabetes was found to be a major risk case of TB recurrence in a cohort of 12,509 pulmonary tuberculosis patients (HR 2.40), male sex, age ≥ 60 and initial etiologic positivity ⁽¹⁵⁾. Likewise, diabetic patients used in our study showed higher ESR and a positive correlation between fasting

blood sugar and ESR, which means diabetes is related to an elevated disease activity and inflammatory load in pulmonary TB.

A project analyzed 1,417 TB patients in which 312 (22%) were diabetic, which experienced more fatigue (58.3% vs 47.5%), weight loss (8.21 ± 6.2 kg vs 5.74 ± 4.0 kg), anemia (88.9% vs 77.6%), and thick-walled cavities that are connected with high uric acid, hemoptysis, and chest pain ⁽¹⁶⁾. Likewise, more weight loss (92.7% vs 70.9%), decreased appetite (90.9% vs 60.0%), fever (100% vs 90.9%), and chronic illness (25.5% vs 5.5%), had more severe systemic manifestations and comorbidities in patients with TB-DM.

Among 327 TB patients, diabetes and hyperglycemia were found to be associated with more widespread lung lesions, cavities and loss of lymphocyte subsets, which decreased as the fasting glucose increased, suggesting failure to respond to the disease and poor disease pathology ⁽¹⁷⁾. In tune with this, fasting glucose, elevated ESR, and increased systemic symptomology were elevated in diabetic TB patients, similar to the previous results, in our cohort.

The 20.5% lower lung field TB among diabetic patients with diabetes (mean age 53.2 ± 14.4) was reported as correlated with smear positivity, elevated ESR (>50 mm/h), and HbA1c ($>7\%$) and as the results of a study of 117 TB patients, involving diabetes (OR 6.81) and age > 40 (OR 3.93) as important risk factors ⁽¹⁸⁾. Likewise, diabetic TB patients in our cohort were older (49.1 averagely 11.8) than non-diabetics, with elevated ESR (23.6% vs 9.1%, clearly above 60mm/hr) and more than half with uncontrolled fasting glucose, which reinforces the importance of age, diabetes, and hyperglycemia in systemic inflammation and severity of the disease.

In one study of 100 rifampicin-sensitive PTB patients, 81 (81%) became negative on AFB smears after two months, and the reductions found in NLR (baseline median 3.5 to 2.1, 83.9% of responders), MLR (0.38 to 0.22, 85.2%) and NMR (7.2 to 4.1, 83.9%) were noted, although non-responders ($n = 19$, 19%) showed no change ⁽¹⁹⁾. In our cohort, diabetic PTB patients had a higher baseline ESR (mean 45.5 mm/hr vs 23.6 mm/hr. in non-diabetics) and elevated total leukocyte counts (mean $10.8 \times 10^9/L$) very suggestive of the high level of systemic inflammation and this also warranted close monitoring.

Another investigation done in 169 patients with TB (mean age 39.3 ± 15.4 years, 72.8% males), higher baseline ESR (mean 42 mm/hr), WBC count (mean $8.7 \times 10^9/L$), neutrophil (mean 65%) and monocyte count (mean $0.7 \times 10^9/L$) and NLR (mean 3.2), and hemoglobin (mean 13.1 g/dL) and lymphocyte percentage, mean 28% predicted greater CT severity post-treatment ⁽²⁰⁾. In our cohort complications of diabetes such as high ESR (mean 45.5 mm/hr.) and altered leukocyte count (mean total WBC $10.8 \times 10^9/L$) were observed by patients with diabetic TB suggesting increased inflammation and immune dysregulation.

This research is limited by its cross-sectional design, a single center, and an intermediate sample, which might limit their generalization and prevent any causal inferences. There was no measure of lifestyle variables, glycemic variability, and long-term outcome. However, the recorded high ESR and its positive linkage with fasting blood sugar indicate that normal inflammatory and metabolic monitoring can be used to diagnosis high-risk TB patients with diabetes so that specific measures can be taken to ensure good clinical outcome through close monitoring and early intercession.

CONCLUSION

The study found that there was a high inverse relationship between neutrophils and lymphocytes in suspected patients of pulmonary tuberculosis regardless of diabetic condition. In diabetic patients, the relationship between poor glycemic control and the increased inflammatory response was found to be significantly positive with fasting blood sugar. Conversely, such correlations were not clear in diabetic patients who showed a normal level of glycemic level.

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